UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/167,715	12/15/93	LAWN R	MSMT 01/CONT

FURMAN, K
EXAMINER

18M2/0614

KILPATRICK & CODY
1100 PEACHTREE ST.
SUITE 2800
ATLANTA, GA 30309-4530

ART UNIT	PAPER NUMBER
1814	12

DATE MAILED: 06/14/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 12-15-93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 4-6, 8 and 20-26 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 1-3, 7 and 9-19 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 4-6, 8 and 20-26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

08/167,715

Part III DETAILED ACTION

OBJECTIONS/REJECTIONS WITHDRAWN

1. The rejection of Claims 4-6 and 8 under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 21 of the last Office Action, is withdrawn in view of the new scope rejection set forth below.

The rejection of Claim 4 under 35 U.S.C. § 103 as being unpatentable over the January 1986 reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al and the reference of Pongor;

the rejection of Claim 5 under 35 U.S.C. § 103 as being unpatentable over January 1986 reference of Guha et al in view of the patent of Weissman et al, the patent of Santerre et al and the reference of Dull et al.;

the rejection of Claim 6 under 35 U.S.C. § 103 as being unpatentable over January 1986 reference of Guha et al in view of the reference of Abstract # 1632 of Morrissey et al, the patent of Weissman et al, the patent of Santerre et al and the reference of Pongor; and

the rejection of Claims 8 under 35 U.S.C. § 103 as being unpatentable over January 1986 reference of Guha et al in view of the reference of Abstract # 1632 of Morrissey et al, the patent of Weissman et al, the patent of Santerre et al and the reference of Dull et al., as set forth in paragraphs 23-26 of the last Office Action, are withdrawn in view of the instant amendments and applicants' arguments that the specification show that applicants had to resort to an adipose tissue gene library to obtain clones and the prior art of record did not appear to suggest that tissue factor was produced in such tissue. Further, the amino acid sequence data of Guha et al. would have lead those of ordinary skill in the art away from tissue factor protein of the sequence of Figure 2.

NEW OBJECTIONS/REJECTIONS

2. Claims 4-6, 8 and 20-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 and those dependent thereon are indefinite because the limitation to "as selected from the group" make the claim indefinite because the term "as" in the limitation "...as selected from the group..." has similar meaning to the terms "for example" and renders the claim indefinite because it is unclear whether the limitation(s) following the term are part of the claimed invention or not, and the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Additionally, claim 4 repeats the term "wherein" in the first two lines of the claim and appears to be a typographical error.

Claim 6 and those dependent thereon are indefinite because the limitation to wherein "an" amino acid has been inserted, deleted or substituted renders the claim unclear with regard to whether one and only one amino acid has been inserted, deleted or substituted or whether at least one amino acid has been inserted, deleted or substituted and the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

Claim 8 is indefinite because there appears to be a missing modifier such as "at" or "positioned at" between "residues" and "about" and the meaning is unclear.

Claim 20 and those dependent thereon are indefinite because it is unclear how a tissue factor, i.e., a protein as oppossed to the DNA, can be thought of as "encoding" an amino acid sequence. Such terminology is incorrect.

Claim 20 and those dependent thereon are also indefinite because the tissue factor having the sequence of Figure 2 is not a soluble protein since it includes the transmembrane region and it is unclear whether the transmembrane

region is intended to be excluded or whether applicants intend to rather claim a "solublized" isolated tissue factor.

Claims 22 is indefinite because the limitation to a product, tissue factor, "consisting essentially of" the sequence set forth is unclear with regard to what variability of the protein is contemplated, i.e. such as only with regard to extensions at one or more ends of the protein or whether the limitations also include any substitutions, deletions, insertions, and chemical derivations which do not materially affect the basic functional properties of the protein.

Claim 23 is indefinite because the limitation to the "first amino acid" of the Figure is unclear with regard to whether the amino acid at position 1 of the sequence is first or the actual first amino acid of the sequences at position -32.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as it is now claimed because it introduces new matter into the specification because the limitation to "at least some" of the region between amino acids residues 243 to 263 in addition to residues 1-219 does not have written descriptive basis in the specification (claim 26). The specification also does not appear to provide written descriptive basis for wherein both the transmembrane

domain and the portion C-terminal thereto (i.e., residues 243 to 263) are deleted (claim 22 and 23) or wherein the specific residues 243 to 263 are deleted or where deletions are specifically selected from these residues or anywhere in positions 220-263 (claims 23 and 26).

> "Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 USC 112, unless there are specific facts which lead to determination that subgenus is implicitly described..." (see Ex parte Westphal, 26 USPQ2d 1858 (BPAI, 1993)).

5. Claim 22, 23 and 26 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. Claims 4-6, 8 and 21-26 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the mature tissue factor protein of Figure 2 and that having a deletion of the transmembrane domain. See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

The specification provides no guidance regarding the sequence similarity or lack thereof with tissue factor from other tissue sources or from other animals. The reference of Guha et al. (see col. 1 of p. 301) discloses a portion of an amino acid of human placental tissue factor which is quite different from that of adipose tissue and brain tissue factor sequence such that DNA probes

encoding the one will not expectedly be of any use in finding the other since there would not be sufficient homology to hybridize under any conditions much less stringent screening conditions. Additionally, in col. 2 of p. 301 Guha et al. disclose that there is poor immunological cross-reactivity of tissue factor proteins between human and other animal (i.e., bovine) sources which would suggest substantial sequence variation between animal species such that it would have been unpredictable whether the disclose DNA would be useful in cloning the tissue factor protein of other animal sources. Thus, it would require undue experimentation to clone other natural forms of tissue factor protein (see Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027; and Ex parte Maizel, 27 USPQ2d 1662 (BPAI, 1993)).

Additionally, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

The reference of Robson et al. (Introduction to Proteins and Protein Engineering) teaches on page 41 that,

> "...it cannot be assumed a priori that changing even one amino acid will not significantly, perhaps even drastically, alter the properties of a protein".

Thus, it is unpredictable whether any of the modifications to which the claims are drawn would be workable in the instant protein, especially in view of the non-conservative nature of the changes, and applicants have provided no evidence or examples to show which changes or the extent thereof which can actually be tolerated in the tissue factor protein. Applicants urge that all the claimed forms have now been made and reported in the literature to have biological activity and that, with the sequence in hand, it would have been routine to modify the sequence. However, these arguments are mere allegations unsupported by evidence and are not persuasive. Regardless of the fact that single amino acid modifications can be screened for, if one skilled in the art does not have the expectation of success in finding functionally equivalent analogs by making these changes then such screening would be undue experimentation. Even if it can be shown that modifications representative of those of the scope of the claims have been made in tissue factor protein since the application was filed, such changes may have been made based on information which was not known or disclosed at the time the invention was made.

Contrary to applicants arguments, while recombinant and mutagenesis techniques are known, it is <u>not</u> routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. The reference of Pongor (1987, Methods in Enzymology, Vol. 154, pages 450-473) teaches that it is "clearly too expensive and time consuming" to make amino acid substitutions at more than one position, even in a particular region of the protein (see p. 450), i.e., in view of the manifold possibilities for change in structure and the uncertainty as to what utility will be possessed by the such muteins. Time and expense (i.e., quantity of

experimentation) is one factor to be considered in determining whether experimentation is "undue" and the teaching of Pongor further evidences that the experimentation required to make up for what the disclosure and prior art lacks is undue in its teaching that the quantity of experimentation is clearly prohibitive, i.e. that **practitioners of the art are not prepared to test and screen recombinant protein muteins having multiple substitutions as a routine means of determining other similar analogs or muteins.** Thus, such experimentation for multiple substitutions is not routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. While Pongor discusses various complex experimental analyses with regard to the multifarious aspects of protein structure/function relationships which might narrow the number of possibilities in production of analogs, these analyses are merely hypothetical and merely provide a basis for further undue experimentation (see p. 473) and applicant has provided no guidance with regard to how these or similar techniques could be used to sufficiently narrow the possibilities for the instant protein. Further, one skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following : (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical to activity; (C) what fragments, if any, of the extracellular domain can be made which retain the biological activity of the intact protein; and (D) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Additionally, "tissue factor protein" (in contrast to what is known in the art as tissue factor) is merely functionally defined as any protein capable of correcting various bleeding disorders and it would clearly require undue experimentation to support the extremely broad scope of such proteins encompassing an essentially infinite number of possible structures and amino acid sequences including those unrelated to the particular disclosed human sequence. It is still not possible to de novo design a protein to perform a particular function on the level of the biological activity of tissue factor protein.

Regarding claim 21, glycosylation is often required for activity and it is unpredicatable whether an unglycosylated form will have tissue factor activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027; Ex parte Maizel, 27 USPQ2d 1662 (BPAI, 1993); and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 20 and 21 are rejected under 35 U.S.C. § 102(a) as being ancticipated by abstract no. 1632 of Morrissey et al. The abstract of Morrissey et al. discloses purified brain tissue factor in glycosylated form and lacking glycosylation (i.e., deglycosylated). While the reference of Morrissey et al. does not disclose the sequence of Figure 2, such is evidenced to have been inherent in the tissue factor of Morrissey et al. by the fact that the brain and adipose source forms are known to have the same sequence (see Edgington et al., (U.S. Patent No. 5,110,730, which discloses human brain tissue factor and is cited as evidence of inherent properties but is not relied upon in the rejection). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

OBJECTIONS/REJECTIONS MAINTAINED

9. Applicant's arguments filed 12-15-94 have been fully considered but they are not deemed to be persuasive.

10. Claims 4, 6 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by the January 1986 reference Guha et al. It is noted that the previous rejection had indicated that the sequence data of the brain form was given by the reference. However, it is now clear from the reference that the sequence data was only for the placenta form.

The reference of Guha et al discloses purified brain and placenta forms of tissue factor and partial amino acid sequence data for tissue factor protein (TF) from human placenta (see whole publication, especially col. 1, 3rd paragraph of p. 301). This sequence differs in at least one amino acid position from the corresponding part of the sequence of the TF of the instant Figure 2. Thus, the placenta TF of Guha et al represents a TF protein where amino acid residues have been at least substituted of the nature to which the claims are limited as evinced by the lack of similarit between sequences. While the reference does not disclose the proteins produced by the claimed process, i.e. where the amino acid(s) are substituted such as by recombinant techniques by the hand of man, the purification or production of a protein by a particular process does not impart novelty or unobviousness to a protein when the same protein is taught by the prior art. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). The brain form is evinced to read upon claim 20 for the reasons discussed above.

Applicants arguments are on the grounds that the instant claims delineate the modifications. However, this is not persuasive for the reasons discussed in the statement of the rejection.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The reference of Edgington et al. (U.S. Patent No.

5,110,730) has a U.S. Priority Date to 3-31-87 discloses the claimed protein and claims the DNA.

Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. The examiner can normally be reached on Monday-Thursday from 7:30 AM-5:00 PM. The examiner can also be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bob Wax, can be reached at (703) 308-4216.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 13, 1994

KEITH C. FURMAN, Ph.D.
PRIMARY EXAMINER
GROUP 1800